



(12) PATENT ABRIDGMENT (11) Document No. AU-B-85418/91
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 647528

(54) Title
TREATMENT PROCESS FOR PROMOTING WEIGHT LOSS EMPLOYING A SUBSTITUTED
DELTA5-ANDROSTENE

(51)⁵ International Patent Classification(s)
A01N 045/00 C07J 001/00 A61K 031/565

(21) Application No. : 85418/91 (22) Application Date : 28.08.91

(87) PCT Publication Number : WO92/03925

(30) Priority Data

(31) Number (32) Date (33) Country
575156 29.08.90 US UNITED STATES OF AMERICA

(43) Publication Date : 30.03.92

(44) Publication Date of Accepted Application : 24.03.94

(71) Applicant(s)
HUMANETICS CORPORATION

(72) Inventor(s)
HENRY ARNOLD LARDY

(74) Attorney or Agent
SPRUSON & FERGUSON, GPO Box 3898, SYDNEY NSW 2001

(56) Prior Art Documents
US 4898694

(57) Claim

1. A treatment method comprising the step of treating a subject in need of such treatment with an effective weight gain preventative amount of $\Delta 5$ -androstene $3\beta,7\alpha,17\beta$ -triol, $\Delta 5$ -androstene $3\beta,17\beta$ -diol-7-one, or a derivative thereof wherein at least one of the hydroxyl groups is esterified with a C_{2-22} aliphatic acid, a C_{7-12} aromatic acid, a C_3 or greater dicarboxylic acid in which only one of the carboxyl groups is esterified to the hydroxyl group(s) on the steroid; or an inorganic acid.

10. A treatment method comprising the step of treating an overweight subject in need of such treatment with an effective weight reduction promoting amount of $\Delta 5$ -androstene $3\beta,7\alpha,17\beta$ -triol, $\Delta 5$ -androstene $3\beta,17\beta$ -diol-7-one, or a derivative thereof wherein at least one of the hydroxyl groups is esterified with a C_{2-22} aliphatic acid, a C_{7-12} aromatic acid, a C_3 or greater dicarboxylic acid in which only one of the carboxyl groups is esterified to the hydroxyl group(s) on the steroid; or an inorganic acid.

11. A method of treating obesity comprising the step of treating an obese subject with a therapeutic amount of $\Delta 5$ -androstene $3\beta,7\alpha,17\beta$ -triol, $\Delta 5$ -androstene $3\beta,17\beta$ -diol-7-one, or a derivative thereof wherein at least one of the hydroxyl groups is esterified with a C_{2-22} aliphatic acid, a C_{7-12} aromatic acid, a C_3 or greater dicarboxylic acid in which only one of the carboxyl groups is esterified to the hydroxyl group(s) on the steroid; or an inorganic acid.

(11) AU-B-85418/91

-2-

(10) 647528

20. A pharmaceutical composition for inhibiting weight gain in a subject comprising a steroid of any one of claims 17 to 19, together with a pharmaceutically acceptable carrier, diluent or adjuvant therefor.

OPI DATE 30/03/92 APPLN. ID 85418 / 91

AOJP DATE 14/05/92 PCT NUMBER PCT/US91/06147

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A01N 45/00, C07J 53/00		A1	(11) International Publication Number: WO 92/03925 (43) International Publication Date: 19 March 1992 (19.03.92)
(21) International Application Number: PCT/US91/06147 (22) International Filing Date: 28 August 1991 (28.08.91) (30) Priority data: 575,156 29 August 1990 (29.08.90) US		(81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CI (OAPI patent), CM (OAPI patent), DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, SD, SE, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent).	
(71) Applicant: HUMANETICS CORPORATION [US/US]: 1107 Hazeltine Gates Boulevard, Chaska, MN 55318 (US). (72) Inventor: LARDY, Henry, Arnold ; 1829 Therstrand Road, Madison, WI 53705 (US). (74) Agents: BYRNE, Linda, M. et al.: Merchant, Gould, Smith, Edell, Welter & Schmidt, 1000 Norwest Center, 55 East Fifth Street, Saint Paul, MN 55101 (US).		Published 647528 With international search report.	
(54) Title: TREATMENT PROCESS FOR PROMOTING WEIGHT LOSS EMPLOYING A SUBSTITUTED Δ5-ANDROSTENE			
(57) Abstract <p>A method for controlling weight gain or promoting weight loss which includes the step of treating a subject with an effective weight gain controlling or weight loss promoting amount of substituted Δ5-Androstene which is biologically effective for controlling weight gain or promoting weight loss and biologically ineffective for promoting the synthesis of sex hormones. Steroids believed to provide the desired weight control/weight loss characteristics include: Δ5-Androstene-3β,7α-diol-17-one, Δ5-Androstene-3β-ol-7,17-dione, Δ5-Androstene-3β,7α,17-triol, Δ5-Androstene-3β,17β-diol-7-one and various derivatives thereof.</p>			

- 1 -

**TREATMENT PROCESS FOR PROMOTING WEIGHT LOSS
EMPLOYING A SUBSTITUTED $\Delta 5$ -ANDROSTENE**

5

Field of the Invention

Broadly, the invention relates to the use of steroids for effecting a desired biological response. Specifically, the invention relates to the use of a 10 substituted dehydroepiandrosterone capable of effecting a variety of beneficial biological responses without inducing the formation of androgen and estrogen hormones which is commonly associated with dehydroepiandrosterone treatment.

15

Background

Dehydroepiandrosterone ($\Delta 5$ -androstene 3 β -hydroxy, 17-one) (hereinafter referenced as DHEA) is a natural steroid produced in the adrenal glands, testes and brain. Dehydroepiandrosterone is an intermediate in the 20 biosynthetic production of estrogen and androgen (sex hormones) from 17 α -hydroxy pregnenolone.

Treatment with DHEA is believed to stimulate various biological responses including promoting weight loss and inducing an increase in the production of the sex 25 hormones androgen and estrogen.

The ability of DHEA to promote weight control is believed to be mediated through enhanced thermogenesis (conversion to heat energy rather than chemical energy such as ATP and/or triacylglycerides). The thermogenic effect 30 of DHEA is believed to result from a stimulation in the synthesis of liver thermogenic enzymes such as mitochondrial glycerol 3-phosphate dehydrogenase (G3P-DH) and cytosolic malic enzyme (ME) which tend to reduce the efficiency of energy metabolism.

35 Unfortunately, DHEA is not useful as a therapeutic agent for controlling weight gain/promoting weight loss

because the dose rate of DHEA necessary to achieve these desired characteristics may also stimulate the production of sex hormones which is associated with various undesired side effects.

Accordingly, a therapeutic agent possessing the weight loss characteristic of DHEA without the associated sex hormone stimulating characteristic would be extremely useful.

Summary of the Invention

A method for controlling weight gain and/or promoting weight loss which includes the step of treating a subject with an effective weight gain controlling and/or weight loss promoting amount of a substituted Δ^5 -Androstene effective for stimulating the desired 10 biological response while ineffective for inducing the synthesis of sex hormones.

According to a first embodiment of this invention there is provided a treatment method comprising the step of treating a subject in need of such treatment with an effective weight gain preventative amount of Δ^5 -androstene $3\beta,7\alpha,17\beta$ -triol, Δ^5 -androstene $3\beta,17\beta$ -diol-7-one, or a derivative thereof wherein at least one of the hydroxyl 15 groups is esterified with a C₂-22 aliphatic acid, a C₇-12 aromatic acid, a C₃ or greater dicarboxylic acid in which only one of the carboxyl groups is esterified to the hydroxyl group(s) on the steroid; or an inorganic acid.

According to a second embodiment of this invention there is provided a treatment method comprising the step of treating an overweight subject in need of such treatment 20 with an effective weight reduction promoting amount of Δ^5 -androstene $3\beta,7\alpha,17\beta$ -triol, Δ^5 -androstene $3\beta,17\beta$ -diol-7-one, or a derivative thereof wherein at least one of the hydroxyl groups is esterified with a C₂-22 aliphatic acid, a C₇-12 aromatic acid, a C₃ or greater dicarboxylic acid in which only one of the carboxyl groups is esterified to the 25 hydroxyl group(s) on the steroid; or an inorganic acid.

According to a third embodiment of this invention there is provided a method of 25 treating obesity comprising the step of treating an obese subject with a therapeutic amount of Δ^5 -androstene $3\beta,7\alpha,17\beta$ -triol, Δ^5 -androstene $3\beta,17\beta$ -diol-7-one, or a derivative thereof wherein at least one of the hydroxyl groups is esterified with a C₂-22 aliphatic acid, a C₇-12 aromatic acid, a C₃ or greater dicarboxylic acid in which only one of the carboxyl groups is esterified to the 30 hydroxyl group(s) on the steroid; or an inorganic acid.

According to a fourth embodiment of this invention there is provided a treatment procedure effective for promoting weight loss which comprises the step of treating an overweight subject with an effect weight reduction promoting amount of Δ^5 -androstene $3\beta,7\alpha,17\beta$ -triol, Δ^5 -androstene $3\beta,17\beta$ -diol-7-one, or a derivative thereof wherein at least 35 one of the hydroxyl groups is esterified with a C₂-22 aliphatic acid, a C₇-12 aromatic acid, a C₃ or greater dicarboxylic acid in which only one of the carboxyl groups is esterified to the hydroxyl group(s) on the steroid; or an inorganic acid.

According to a fifth embodiment of this invention there is provided a treatment method comprising the step of treating a subject in need of such treatment with an

effective weight gain preventative amount of $\Delta 5$ -androstene 3β -ol-7,17-dione, $\Delta 5$ -androstene $3\beta,7$ -diol-17-one, or a derivative thereof wherein at least one of the hydroxyl groups is esterified with a C_{2-22} aliphatic acid, a C_{7-12} aromatic acid, a C_3 or greater dicarboxylic acid in which only one of the carboxyl groups is esterified to the hydroxyl group(s) on the steroid; or an inorganic acid.

According to a sixth embodiment of this invention there is provided a treatment method comprising the step of treating a subject in need of such treatment with an effective weight reduction promoting amount of $\Delta 5$ -androstene 3β -ol-7,17-dione, $\Delta 5$ -androstene $3\beta,7$ -diol-17-one, or a derivative thereof wherein at least one of the hydroxyl groups is esterified with a C_{2-22} aliphatic acid, a C_{7-12} aromatic acid, a C_3 or greater dicarboxylic acid in which only one of the carboxyl groups is esterified to the hydroxyl group(s) on the steroid; or an inorganic acid.

According to a seventh embodiment of this invention there is provided a method of treating obesity comprising the step of treating an obese subject with a therapeutic amount of $\Delta 5$ -androstene 3β -ol-7,17-dione, $\Delta 5$ -androstene $3\beta,7$ -diol-17-one, or a derivative thereof wherein at least one of the hydroxyl groups is esterified with a C_{2-22} aliphatic acid, a C_{7-12} aromatic acid, a C_3 or greater dicarboxylic acid in which only one of the carboxyl groups is esterified to the hydroxyl group(s) on the steroid; or an inorganic acid.

According to an eighth embodiment of this invention there is provided a treatment procedure effective for promoting weight loss which comprises the step of treating an overweight subject with an effective weight reduction promoting amount of $\Delta 5$ -androstene 3β -ol-7,17-dione, $\Delta 5$ -androstene $3\beta,7$ -diol-17-one, or a derivative thereof wherein at least one of the hydroxyl groups is esterified with a C_{2-22} aliphatic acid, a C_{7-12} aromatic acid, a C_3 or greater dicarboxylic acid in which only one of the carboxyl groups is esterified to the hydroxyl group(s) on the steroid; or an inorganic acid.

According to a ninth embodiment of this invention there is provided a biologically active steroid effective for inhibiting weight gain without inducing a suppression of the appetite or promoting the synthesis of sex hormones comprising $\Delta 5$ -androstene $3\beta,7\alpha,17\beta$ -triol, or a derivative thereof wherein at least one of the hydroxyl groups is esterified with a C_{2-22} aliphatic acid, a C_{7-12} aromatic acid, a C_3 or greater dicarboxylic acid in which only one of the carboxyl groups is esterified to the hydroxyl group(s) on the steroid; or an inorganic acid.

According to a tenth embodiment of this invention there is provided a biologically active steroid effective for inhibiting weight gain without inducing a suppression of the appetite or promoting the synthesis of sex hormones comprising $\Delta 5$ -androstene $3\beta,17\beta$ -diol-7-one, or a derivative thereof wherein at least one of the hydroxyl groups is esterified with a C_{2-22} aliphatic acid, a C_{7-12} aromatic acid, a C_3 or greater dicarboxylic acid in which only one of the carboxyl groups is esterified to the hydroxyl group(s) on the steroid; or an inorganic acid.

According to an eleventh embodiment of this invention there is provided a treatment method comprising the step of treating a subject in need of such treatment with an effective amount of a steroid of the ninth or tenth embodiment of this invention.

Steroids believed to provide the desired beneficial biological results include:

5 Δ5-Androstene-3β,7α-diol-17-one
Δ5-Androstene-3β-ol-7,17-dione
Δ5-Androstene-3β-7α,17-triol
Δ5-Androstene-3β-17β-diol-7-one

and derivatives thereof wherein (i) at least one of the hydroxyl groups is esterified with an
10 acid selected from the group consisting of (i) C₂₋₂₂ aliphatic acids that may or may not
contain one or more double bonds and may or may not contain branched carbon chains,
(ii) C₇₋₁₂ aromatic acids, (iii) C₃ or larger dicarboxylic acids in which only one of the
carboxyl groups is esterified to the hydroxyl group(s) on the steroid leaving the second
carboxyl group free or in the form of a salt, or (iv) inorganic acids such as sulfuric and
15 phosphoric.

These steroids may also be administered as carbamates, enanthates and other
derivatives capable of releasing the free steroid in the intestinal tract, the

- 3 -

blood or in tissues. The desired biological activity is a function of the steroid moiety. Derivation of the moiety may serve a variety of possible functions including stabilization of the steroid, flavoring or obscuring the 5 natural flavor of the steroid, or affecting the rate of absorption of the steroid.

*Detailed Description of the Invention
Including a Best Mode*

10 $\Delta 5$ -Androstene substituted at C-3, C-7 and/or C-17 with a hydroxyl or keto group are biologically effective for controlling weight gain and promoting weight loss without substantial stimulation in the production of sex hormones. Derivatives of these substituted $\Delta 5$ -Androstene 15 in which at least one of the hydroxyl groups is esterified with an acid selected from the group consisting of (i) C₂₋₂₂ aliphatic acids that may or may not contain one or more double bonds and may or may not contain branched carbon chains, (ii) C₇₋₁₂ aromatic acids, (iii) C₃ or larger 20 dicarboxylic acids in which only one of the carboxyl groups is esterified to the hydroxyl group(s) on the steroid leaving the second carboxyl group free or in the form of a salt, or (iv) inorganic acids such as sulfuric and phosphoric, and also believed to possess the desired 25 characteristics.

These steroids may also be administered as carbamate, enanthates and other derivatives capable of

- 4 -

releasing the free steroid in the intestinal tract, the blood or in tissues. The desired biological activity is a function of the steroid moiety; the derivatizing moiety may serve to stabilize the steroid, to favor or to retard 5 absorption or to obscure its flavor.

Synthesis

Δ5-Androstene 3β,7-diol, 17-one
(7-hydroxy DHEA)

10 Δ5-Androstene 3β,7α-diol, 17-one (7-hydroxy DHEA)
can be synthesized from commercially available DHEA acetate
by sequentially synthesizing:

15 Δ5-Androstene-3β hydroxy-17-one
Δ5-Androstene-3β-hydroxy-7-bromo-17-one
Δ5-Androstene-3β,7α-hydroxy-17-one diacetate
Δ5-Androstene-3β,17α-hydroxy-17-one

Δ5-Androstene 3β-hydroxy-7-bromo-17-one (7-bromo
DHEA) can be synthesized from Δ5-Androstene 3β-hydroxy-17-
one acetate (DHEA acetate) by reacting the DHEA acetate
20 with a brominating agent such as Dibromantin (1,3 dibromo
5,5 dimethylhydantoin or N-bromo succinimide. 7-bromo DHEA
is unstable and must be used immediately in the next step
of the process.

The 7-bromo DHEA containing an isomeric mixture of
25 7α-bromo DHEA and 7β-bromo DHEA may be equilibrated to 7α-
bromo DHEA in accordance with the method described for a
cholesterol derivative in Confalone, P.N., Kulesha, I.D.,
and Uskokovic, M.R. Jour. Org. Chem., vol. 46, pp 1030-1032

- 5 -

(1981). Briefly the racemic mixture of 7-bromo DHEA is contacted with cold anhydrous LiBr and shielded from light until their stereospecific composition is achieved.

5 $\Delta 5$ -androstene 3β , 7-hydroxy-17-one diacetate ($\Delta 5$ -hydroxy DHEA diacetate) may be synthesized from the 7-bromo DHEA by reacting the 7-bromo DHEA with a mixture of glacial acetic acid and powdered silver acetate at room temperature in a suitable solvent such as methylene chloride or acetone.

10 $\Delta 5$ -androstene 3β , 7α -hydroxy-17-one diacetate (DHEA) 2 may be synthesized from the 7-hydroxy DHEA diacetate by reacting the 7-hydroxy DHEA diacetate dissolved in methanol with an aqueous solution containing a suitable base such as Na_2CO_3 .

15 The synthesized 7-hydroxy DHEA may then be purified by (i) evaporating the methanol in vacuo, (ii) extracting the 7-hydroxy DHEA into an appropriate organic solvent such as dichloromethane, (iii) evaporating the organic solvent in vacuo, (iv) azeotropically drying the 20 extracted solids containing the 7-hydroxy DHEA with a suitable organic solvent such as ethanol, (v) dissolving the extracted solids in acetone, and then (vi) adding a suitable precipitating agent, such as hexane, to the acetone solution to produce purified crystals of $\Delta 5$ -
25 Androstene $3\beta, 7\alpha$ -diol, 17-one.

- 6 -

A second crop of Δ^5 -Androstene $3\beta,7\alpha$ -diol, 17-one
crystals may be obtained by cooling the resultant solution
below room temperature.

5

Δ^5 -Androstene- 3β -ol 7,17-dione
(7-keto DHEA)

Δ^5 -Androstene 3β -ol, 7,17-dione can be synthesized
10 from commercially available DHEA acetate by sequentially
synthesizing:

3β -acetoxy- Δ^5 -androstene-17-one
 3β -acetoxy- Δ^5 -androstene-7,17-one
 Δ^5 -androstene 3β -hydroxy-7,17-one

15 3β -acetoxy- Δ^5 -androstene-7,17-one (7-one DHEA
acetate) can be synthesized from 3β -acetoxy- Δ^5 -androstene-
17-one (DHEA acetate) by reacting the DHEA acetate with the
oxidizing agent CrO_3 , in accordance with the procedure
outlined in Fieser, L.F., Jour. Am. Chem. Soc., vol. 75, pp
20 4386-4394 (1953).

Δ^5 -androstene 3β -hydroxy-7,17-dione (7-one DHEA)
can be synthesized from the 7-one acetate and purified by
employing the deesterification and purification steps set
forth above with respect to the synthesis and purification
25 of 7-hydroxy DHEA from 7-hydroxy DHEA diacetate.

- 7 -

Δ5-Androstene 3 β , 7 α , 17 β -triol
(7 α -hydroxy Androstenediol)

Δ5-Androstene 3 β , 7 α , 17 β -triol can be synthesized from commercially available Androstenediol diacetate by 5 sequentially synthesizing:

Δ5-androstene 3 β , 17 β -diol, diacetate
Δ5-androstene 3 β , 17 β -diol-7-b-omide, diacetate
Δ5-androstene 3 β , 7 α , 17 β -triol-3, 17-diacetate
Δ5-androstene 3 β , 7 α , 17 β -triol

10 Δ5-androstene 3 β , 17 β -diol-7-bromide (7-bromo Androstenediol) can be synthesized from the commercially available Δ5-androstene 3 β , 17 β -diol diacetate (Androstenediol diacetate) by reacting the Androstenediol diacetate with a brominating agent such as Dibromantin (1,3 dibromo 5,5 dimethylhydantion) or N-bromosuccinimide. The 15 synthesized 7-bromo Androstenediol is unstable and must be used immediately.

The 7-bromo Androstenediol contains an isomeric mixture of 7 α -bromo Androstenediol and 7 β -bromo Androstenediol which can be equilibrated to 7 α -bromo Androstenediol in accordance with the method described in 20 Confalone, P.N., Kulesha, I.D., and Uskokovic, M.R. Jour. Org. Chem., vol. 46, pp 1030-1032 (1981). Briefly the racemic mixture of 7-bromo Androstenediol is contacted with 25 anhydrous LiBr and shielded from light until the stereospecific composition is achieved.

Δ5-androstene 3 β , 7 α , 17 β -triol-3, 17-diacetate (7-hydroxy Androstenediol diacetate) may be synthesized from

- 8 -

the 7-bromo Androstenediol by reacting the 7-bromo Androstenediol with a mixture of glacial acetic acid and silver acetate in a suitable solvent such and methylene chloride or acetone.

5 Δ^5 -androstene $3\beta,7\alpha,17\beta$ -triol (7-hydroxy Androstenediol) may by synthesized from the 7-hydroxy Androstenediol diacetate by reacting the 7-hydroxy Androstenediol diacetate in methanol with an aqueous solution containing a suitable base such as Na_2CO_3 .

10 The synthesized 7-hydroxy Androstenediol may then be purified by (i) evaporating the methanol in vacuo, (ii) extracting the 7-hydroxy Androstenediol into an appropriate organic solvent such as dichloromethane, (iii) evaporating the organic solvent in vacuo, (iv) azeotropically drying 15 the extracted solids containing the 7-hydroxy Androstenediol with a suitable organic solvent such as ethanol, (v) dissolving the extracted solids in acetone, and then (vi) adding a suitable precipitating agent, such as hexane, to the acetone sclution to produce purified 20 crystals of Δ^5 -Androstene $3\beta,7\alpha,17\beta$ -triol.

A second crop of Δ^5 -Androstene $3\beta,7\alpha,17\beta$ -triol crystals may be obtained by cooling the resultant solution below room temperature.

- 9 -

$\Delta 5$ -Androstene $3\beta,17\beta$ -diol, 7-one
(7-keto Androstenediol)

$\Delta 5$ -Androstene $3\beta,17\beta$ -dic1-7-one can be
synthesized from commercially available androstenediol
5 diacetate by sequentially synthesizing:

$\Delta 5$ -androstene $3\beta,17\beta$ -diol diacetate
 $\Delta 5$ -androstene $3\beta,17\beta$ -diol-7-one diacetate
 $\Delta 5$ -androstene $3\beta,17\beta$ -diol-7-one

$\Delta 5$ -androstene $3\beta,17\beta$ -diol-7-one diacetate can be
10 synthesized from $\Delta 5$ -androstene $3\beta,17\beta$ -diol diacetate
(Androstenediol diacetate) by reacting the androstenediol
diacetate with the oxidizing agent CrO_3 in accordance with
the procedure outlined in Fieser, L.F., Jour. Am. Chem. Soc., vol. 75, pp 4386-4394 (1953).

15 $\Delta 5$ -androstene $3\beta,17\beta$ -diol-7-one (7-one
androstenediol) can be synthesized from $\Delta 5$ -androstene
 $3\beta,17\beta$ -diol-7-one diacetate and purified by employing the
deesterification and purification steps set forth above
with respect to the synthesis and purification of 7-hydroxy
20 DHEA from 7-hydroxy DHEA diacetate.

Without intending to be unduly limited thereby, it
is believed that the substituted $\Delta 5$ -Androstene may be
further modified by esterifying one or more of the hydroxyl
groups with any of a variety of organic acids and inorganic
25 acids such as sulfuric or phosphoric acid.

- 10 -

Treatment

A subject may be treated with the substituted $\Delta 5$ -Androstene by any of the commonly accepted practices including orally or by injection. It is believed that 5 treatment at a dosage rate of about 0.1 to 2 grams, preferably about 0.5 to 2 grams, steroid per 100 kilograms body weight per day is generally effective for promoting weight loss and/or preventing weight gain. A dose rate of less than 0.1 gram per 100 kilograms bodyweight is believed 10 to be generally ineffective for preventing weight gain while a dose rate of greater than about 2 grams per 100 kilograms bodyweight increases the cost of the treatment without providing a corresponding benefit in performance. The optimum dose rate to be administered to a subject is case 15 specific as the optimum dose rate depends upon several factors including current body composition (percent fat), the desired effect (weight gain prevention versus weight loss), eating habits of the individual (daily caloric intake), and the like. As would be expected, the dose rate 20 provided to a subject for the purpose of promoting weight loss will be greater than that necessary to promote weight maintenance assuming identical caloric intake under each program.

Without intending to be limited thereby, we 25 believe that the substituted $\Delta 5$ -Androstene are metabolic intermediates between the conversion of DHEA to a

- 11 -

intermediate between the conversion of DHEA to a metabolite(s) actually responsible for enhancing the production of thermogenic enzymes such as glycerol 3-phosphate dehydrogenase and malic enzyme.

5 The subject may be treated with a steroid on any desired schedule. It is anticipated that the steroid will be effective for preventing weight gain and/or promoting weight loss not only while actively present within the body, but also for as long as the concentration of the
10 induced thermogenic enzyme(s) remain elevated. At the present time, the duration of effectiveness for the steroid is not fully appreciated. However, it is believed that the steroid is not stored within the body and will be substantially removed and/or deactivated within days after
15 administration. Accordingly, the subject should be conveniently treated every day for optimum performance but may be treated less frequency such as every other day or week when less than maximum performance is acceptable. For example, a subject placed on a weight maintenance program
20 may require treatment with the steroid thermogenic enzyme(s) are not retained during the entire period between treatments as the weight loss occurring within the first few days after treatment counterbalances any weight gain occurring during the remaining days between treatments.
25 As is apparent from the factors which affect dosage and dose rate, each particular subject should be

- 12 -

carefully and frequently reviewed and the dosage and/or dose rate altered in accordance with the particular situation.

5

*Experimental**Example I*Synthesis Δ^5 -Androstene 3 β ,7 α -diol-17-one

10 (Step 1) Into a two liter, triple neck, round bottom flask equipped with a magnetic stirrer and a reflux condenser was placed 1000 ml hexane (b.p 69-71°), 10 grams (0.03 moles) DHEA acetate and 13.6 grams (0.16 moles) 15 NaHCO_3 to form a first solution. The first solution was placed under a N_2 atmosphere and heated under constant agitation to reflux. Into the refluxing first solution was added 6.11 grams (0.021 moles) Dibromantin (1,3 dibromo 5,5 dimethylhydantion) as a brominating agent to form a second 20 solution. The second solution gradually turned orange after which it rapidly turned a pale white/yellow. The second solution was refluxed for 30 minutes, cooled to room temperature and filtered through a sintered glass funnel. The residue was rinsed with 50 ml dichloromethane and the 25 combined filtrate rotovapped to dryness at a temperature of less than 35°C. The dry filtrate (Δ^5 -Androstene 3 β -ol-7-bromo-17-one) is unstable to storage and was used immediately in step two.

- 13 -

(Step 2) The dry filtrate was resolubilized in 80 ml of dichloromethane in a one liter stoppered flask equipped with a magnetic stirrer and placed in an ice bath. Into the resolubilized filtrate was added 8 grams anhydrous 5 LiBr in 320 ml ice-cold acetone to form a third solution. The third solution was shielded from light and stirred continuously for three hours. The resulting solution was predominantly (Δ 5-Androstene 3β -ol- 7α -bromo-17-one) was allowed to warm briefly and used immediately in step three.

(Step 3) Into a 500 ml flask equipped with a magnetic stirrer was placed 320 ml dichloromethane, 80 ml glacial acetic acid, and 26 grams of silver acetate to form a first suspension. The first suspension was stirred continuously for 20 minutes at room temperature. The 15 stirred first suspension was added under constant agitation into the warmed solution of predominantly Δ 5-Androstene 3β -ol- 7α -bromo-17-one to form a second suspension. The second suspension was constantly stirred for 30 minutes at room temperature during which the suspension was filtered 20 through a sintered glass funnel to produce a solid fraction. The filtered solid fraction was rinsed with 100 ml dichloromethane. The filtrate was extracted three times with 1000 ml of water, neutralized with 1000 ml of a 5% NaHCO₃ solution, and extracted twice more with water. The 25 organic solution containing Δ 5-Androstene 3β - 17α -diol-17-one diacetate was then rotovapped to dryness.

- 14 -

(Step 4) The dried extracted solids were resolubilized in 500 ml methanol in a one liter, triple necked flask equipped with a magnetic stirrer and a reflux condenser to form a fourth solution. The fourth solution 5 was placed under a N₂ atmosphere and heated under constant stirring to reflux. Into the fourth solution was added 250 ml of a 5% aqueous solution of Na₂CO₃ to form a fifth solution. The fifth solution was refluxed under constant agitation for 45 minutes. The methanol was rotovapped off 10 and the aqueous fifth solution carefully brought to a pH of 7 with an appropriate amount of glacial acetic acid. The neutralized fifth solution was extracted twice with 100 ml of dichloromethane. The dichloromethane solution of $\Delta 5$ -Androstene 3 β ,7 α -diol-17-one was rotovapped to near 15 dryness, azeotropically dried with absolute ethanol, and then azeotropically dried twice with acetone. Warm acetone was added to the dried extracted solids until the solids were completely dissolved to form a sixth solution. Hexane was added to the sixth solution until the solution began to 20 cloud at which time crystals of $\Delta 5$ -Androstene 3 β -7 α -diol-17-one began to form at room temperature.

A second crop of $\Delta 5$ -Androstene 3 β -7 α -diol-17-one crystals was obtained by cooling the remaining sixth solution.

- 15 -

The product melts at about 187-189°C and when recrystallized from acetone/hexane melts at about 192-193°C.

5 **Example II**

Synthesis

Δ^5 -Androstene 3β - $7(\alpha\beta)$ -diol-17-one

Δ^5 -Androstene 3β - 7α -diol-17-one was manufactured in accordance with the procedure set forth in Example I except that Step 2 was eliminated with the dried filtrated from Step 1 simply resolubilized in the 80 ml of dichloromethane in preparation for Step 3.

- 16 -

Example III

Synthesis
 $\Delta 5$ -Androstene 3β -ol-7,17-dione

5 (Step 1) Into a 50 ml flask equipped with a magnetic stirrer and a water bath was placed 6.5 ml acetic anhydride, 23 ml acetic acid, 1.7 grams sodium acetate, and 2 grams DHEA acetate to form a first mixture. Into the first mixture was added 2 grams chromium trioxide over a 10 thirty minute period to form a second mixture. The first mixture was maintained at a constant temperature of 56-58°C and continuously agitated during addition of the chromium trioxide. The second mixture was maintained at 56-58°C and continuously agitated for an additional hour after which 15 the second mixture was cooled and slowly poured under continuous agitation into 600 ml of ice water to form a precipitate. The flocculent precipitate was collected on a sintered glass funnel and washed with water until no longer green. After drying in vacuo over P_2O_5 , the product was 20 dissolved in methanol and recrystallized to yield substantially pure $\Delta 5$ -Androstene 3β -acetoxy-7,17-dione having a melting point of about 191-192°C.

(Step 2) The precipitate was resolubilized in 500 ml of methanol in a one liter, triple necked, round bottom 25 flask equipped with a magnetic stirrer and reflux condenser to form a third solution. The third solution was placed under a N_2 atmosphere and heated under constant agitation

- 17 -

to reflux. Into the third solution was added 250 ml of a 5% solution of Na_2CO_3 , to form a fourth solution. The fourth solution was refluxed under constant agitation for 45 minutes. The methanol was rotovapped off and the 5 aqueous fourth solution carefully brought to a pH of 7 with an appropriate amount of glacial acetic acid. The neutralized fourth solution was extracted with two 100 ml portions of dichloromethane, and two portions combined, and the dichloromethane evaporated in vacuo. The extracted 10 solids were then azeotropically dried first with absolute ethanol and then with two separate portions of acetone. Methanol was added to the dried extracted solids until the solids were completely dissolved to form a fifth solution. Hexane was added to the fifth solution until the solution 15 began to cloud at which time crystals of Δ^5 -Androstene 3β -ol-7,17-dione began to form at room temperature.

A second crop of Δ^5 -Androstene 3β -ol-7,17-dione crystals was obtained by cooling the remaining sixth solution.

20 The resultant product had a melting point of about 235-238°C.

Example IV

25

Synthesis
 Δ^5 -Androstene 3β ,7,17-triol

(Step 1) Into a two liter round bottom flask equipped with a magnetic stirrer and a reflux condenser was

- 18 -

placed 1000 ml hexane (b.p 69-71°), 10 grams (0.03 moles) Δ5-Androstene 3β-17β-diol diacetate and 13.6 grams (0.16 moles) NaHCO₃ to form a first solution. The first solution was placed under a N₂ atmosphere and heated under constant 5 agitation to reflux. Into the refluxing first solution was added 6.11 g (0.021 moles) Dibromantin (1,3-dibromo-5,5-dimethylhydantion) as a brominating agent to form a second solution. The second solution gradually turned orange after which it rapidly turned a pale white/light yellow.

10 The second solution was refluxed for 30 minutes, cooled to room temperature and filtered through a sintered glass funnel. The residue was rinsed with 50 ml dichloromethane and rotovapped to dryness at a temperature of less than 35°C. The dry filtrate (Δ5-Androstene 3β-17β-diol-7- 15 bromide) is unstable to storage and was used immediately in step two.

(Step 2) The dried filtrate was resolubilized in 80 ml of dichloromethane in a flask equipped with a magnetic stirrer and placed in an ice bath. Into the 20 resolubilized filtrate was added 8 g anhydrous LiBr in 320 ml ice-cold acetone to form a third solution. The third solution was shielded from light and stirred continuously for three hours. The resulting solution of predominantly Δ5-Androstene 3β-17β-diol-7α-bromide was allowed to warm 25 briefly and used immediately.

- 19 -

(Step 3) Into a 500 ml flask equipped with a magnetic stirrer was placed 320 ml methylene chloride, 80 ml glacial acetic acid, and 26 grams silver acetate to form a first suspension. The first suspension was stirred 5 continuously for 20 minutes at room temperature. The stirred first suspension was added under constant agitation to the warmed solution of predominantly Δ^5 -Androstene 3β - 17β -diol- 7α -bromide to form a second suspension. The second suspension was constantly stirred for 30 minutes at 10 room temperature during which the suspension gradually darkened and was then filtered through a sintered glass funnel. The residual solids retained on the glass filter were rinsed with 10 ml dichloromethane. The filtrate was extracted three times with 1000 ml of water, neutralized 15 with 1000 ml of a 5% NaHCO₃ solution, and then extracted from the filtrate (Δ^5 -Androstene 3β , 7α , 17β -triol- 3 , 17 -diacetate) were rotovapped to dryness.

(Step 4) The dried extracted solids were resolubilized in 500 ml methanol contained in a one liter, 20 triple necked, round bottom flask equipped with a magnetic stirrer and a reflux condenser to form a fourth solution. The fourth solution was placed under a N₂ atmosphere and heated under constant agitation to reflux. Into the fourth solution was added 250 ml of a 5% aqueous solution of 25 Na₂CO₃ to form a fifth solution. The fifth solution was refluxed under constant agitation for 45 minutes. The

- 20 -

methanol was rotovapped off and the aqueous fifth solution carefully brought to a pH of 7 with an appropriate amount of glacial acetic acid. The neutralized fifth solution was extracted twice with 100 ml dichloromethane and the 5 combined extract evaporated in vacuo. The extracted solids (Δ^5 -Androstene $3\beta,7\alpha,17\beta$ -triol) were azeotropically dried with absolute ethanol and then twice with acetone. Warm acetone was added to the dried extracted solids until the 10 solids were completely dissolved to form a sixth solution. Hexane was added to the sixth solution until the solution began to cloud at which time crystals of Δ^5 -Androstene 15 $3\beta,7\alpha,17\beta$ -triol began to form at room temperature.

A second crop of Δ^5 -Androstene $3\beta,7\alpha,17\beta$ -triol crystals was obtained by cooling the remaining sixth 15 solution.

Example V

Synthesis

Δ^5 -Androstene $3\beta,7(\alpha\beta),17\beta$ -triol

20 Δ^5 -Androstene $3\beta,7(\alpha\beta),17\beta$ -triol was manufactured in accordance with the procedure set forth in Example III except that Step 2 was eliminated with the dried filtrated from Step I simply resolubilized in the 80 ml of methylene 25 chloride in preparation for Step 3.

- 21 -

Example VI

Synthesis

Δ^5 -Androstene $3\beta,17(\beta)$ -diol-7-one

5 (Step 1) Into a 50 ml flask equipped with a magnetic stirrer and a water bath was placed 6.5 ml acetic anhydride, 23 ml acetic acid, 1.7 grams sodium acetate, and 2 grams androstenediol diacetate to form a first mixture. Into the first mixture was added 2 grams chromium trioxide over a thirty minute period to form a second mixture. The first mixture was maintained at a constant temperature of 56-58°C and continuously agitated during addition of the chromium trioxide. The second mixture was maintained at 56-58°C and continuously agitated for an additional hour 10 after which the second mixture was cooled and slowly poured under continuous agitation into 600 ml of ice water to form a precipitate. The flocculent precipitate was filtered through a sintered glass funnel, washed with water until no 15 longer green and dried in vacuo.

20 (Step 2) The dried precipitate was resolubilized in 500 ml of methanol in a one liter, round bottom flask equipped with a magnetic stirrer and reflux condenser to form a third solution. The third solution was placed under a N_2 atmosphere and heated under constant agitation to 25 reflux. Into the third solution was added 250 ml of a 5% aqueous solution of Na_2CO_3 to form a fourth solution. The fourth solution was refluxed under constant agitation for 45 minutes. The methanol was rotovapped off and the

- 22 -

aqueous fourth solution carefully brought to a pH of 7 with an appropriate amount of glacial acetic acid. The neutralized fourth solution was extracted twice with 100 ml portions of dichloromethane and the combined extract 5 evaporated in vacuo. The extracted solids were then azeotropically dried first with absolute ethanol and then twice with acetone. Methanol was added to the dried extracted solids until the solids were completely dissolved to form a fifth solution. Hexane was added to the fifth 10 solution until the solution began to cloud at which time crystals of $\Delta 5$ -Androstene $3\beta 17\beta$ -diol-7-one began to form at room temperature.

The resultant product had a melting point of about 200-202°C.

15

Example VII

Enzymatic Activity
Protocol

20 Administration of Hormone: Male Sprague Dawley rats weighing 125-150 gm were obtained from Sasco Inc. of Oregon, WI. The rats were allowed free access to water and Purina Rat Chow pellets for the first day after arrival. Administration of the steroids began on day two. The 25 steroids were either administered orally (combined with the Purina Rat Chow) or injected intraperitoneal as set forth in Table 1 for 6 days.

- 23 -

Preparation of Liver Mitochondria and Cytosol. The treated rats were sacrificed by decapitation after 6 days of treatment. The livers were excised, placed in 10 ml of a buffer consisting of 250 mM mannitol, 70 mM sucrose, and 3 mM Hepes (hereinafter MSH buffer) at pH 7.4, weighted, removed from the buffer, minced with scissors, washed with MSH buffer, suspended in MSH buffer at a ratio of 1 gram minced liver to 5 ml MSH buffer at a ratio of 1 gram minced liver to 5 ml MSH buffer, and homogenized with a Potter-10 Elvehjem rotary homogenizer.

The Mitochondria fraction was prepared by the method described in Johnson, D. and Lardy, H.A., Methods Enzymology, vol. 10, pp 94-96 (1967) which is hereby incorporated by reference. Briefly, liver homogenate was 15 centrifuged in a Beckman Model J2-21 centrifuge, JA-20 rotor at 750g for 10 minutes and the resulting supernatant solution centrifuged at 15,000g for an additional 10 minutes. The resulting mitochondrial pellets were washed twice with MSH buffer, resuspended in 0.8 to 1 ml of a 35 20 wt% aqueous glycerol solution, and stored at -70°C.

The Cytosolic fraction was obtained by recentrifuging the previously centrifuged supernatant solution at 100,000g for 30 minutes in a Beckman Model L2 ultracentrifuge, type 40 rotor. The resultant supernatant 25 solution was stored at -70°C.

- 24 -

Protein concentrations in the resultant preparations were determined by the Biuret method described in Layne E., Methods Enzymology, vol. 3, pp 450451 (1957) which is hereby incorporated by reference. Briefly, the 5 protein concentrations were determined by treating a dilute protein solution with copper tartrate solution and measuring the optical density at 540 nm.

Enzyme Assays. Mitochondrial G3P-DH activity was measured by the method described in Wernette, M.E., Ochs, 10 R.S., and Lardy, H.A., J. Biol. Chem., vol. 256, pp 12767-12771 (1981) which is a modified version of the method described in Gardner, R.S., Anal. Biochem., vol. 59, pp 272-276 (1974). Both references are hereby incorporated by reference. Briefly, aliquots of the previously prepared 15 mitochondria containing 0.1 to 0.2 mg of protein were incubated in a test tube containing 50 mM sn-glycerol-3-P, 50 mM potassium phosphate (pH 7.0), 1 mM KCN, and 0.2% p-iodonitrotetrazolium violet in a total volume of 0.4 ml for 30 minutes at 37°C. The incubating mitochondria were 20 continuously agitated during the incubation period by a Dubnoff shaker agitated at 100 cycles/min. Incubation was ceased by the addition of 0.6 ml of 1 M acetic acid to the test tube. The iodoformazan formed during the incubation period was extracted into 2 ml of ethyl acetate by adding 25 the ethyl acetate to the test tube, mixing thoroughly, then decanting the ethyl acetate containing the iodoformazan

- 25 -

from the test tube. The optical densities of the iodoformazan containing ethyl acetate layers were read at 490 nm by means of an On Line Instrument Systems, Model 3820 Data System, Spectrophotometry, Cary - 15, Version 5 4.08. An extinction coefficient value of $2.01 \times 10^4 / (M \text{ cm})$ for the iodoformazan product in ethyl acetate was used to calculate enzyme activities.

Cytosolic malic enzyme activity was measured in accordance with the method described in Hsu, R.Y. and 10 Lardy, H.A., Methods Enzymol., vol. 8, pp 230-235 (1967). Briefly, aliquots of the previously prepared cytosol containing 0.1 to 0.5 mg of protein were incubated in a test tube containing 0.8 mM malate, 67 mM triethanolamine buffer (pH 7.4), 4 mM MnCl₂, and 0.2 mM NADP in a total 15 volume of 1 ml for 3 min at 26°C. the incubating cytosol was continuously agitated during the incubation period by a Dubnoff shaker agitated at 100 cycles/min. Activity of malic enzyme was calculated from the rate of change in optical density measured at 340 nm from 0.5 to 2 minutes 20 with an On Line Instrument Systems, Model 3820 Data System, Spectrophotometry, Cary - 15, Version 4.08.

Results of several tests conducted in accordance with the protocol established above are set forth in Table 1.

Table 1
(Enzyme induction in rat liver by C₁₉ steroids)

<u>Steroids</u>	# rats	wt % steroid in diet	G3P-DH (% control)		Malic Enzyme (% control)
			1	2	
Δ ₅ Androstone 3β-ol-17-one (DHEA)	1	0.2	380	512	---
	29	0.1	265	394	---
	27	0.1	---	337	64
	12	0.05	251	337	
	3	0.01	139	220	
Δ ₅ Androstone 3β,7α-ol-17-one (7α-dihydroxy DHEA)	2	0.05	292	423	374
	2	0.03	308	417	118
Δ ₅ Androstone 3β,7α,19-ol-17-one (7α,19-dihydroxy DHEA)	3	0.1	117	220	350
Δ ₅ -Androstone 3β-ol-7,17-one (7-keto DHEA)	3	0.1	439	449	341
	2	0.0575	224	341	229
	3	0.01	183	229	
Δ ₅ -Androstone-3β-ol-7,17-one acetate (7-keto DHEA acetate)	3	0.115	261	447	121
	3	0.1	91	227	611
Δ ₅ -Androstone 3β-ol-7-methyl-17-one (7-methyl DHEA)	3	0.1	99	108	1030
Δ ₅ -Androstone 3β,7α,17β-triol	2	0.01	360	105	175
Δ ₅ -Androstone 3β-17β-diol-7-one	2	0.1	180	452	119
Δ ₅ -Androstone 1β,17β-diol-7-one diacetate	3	0.13	232	452	
	2	0.01	173	119	

1 Control activity based upon enzyme activity in the livers of rats fed with the stock diet without hormone supplement. In each assay, control rats fed only stock diet without hormone supplement were compared with test rats fed stock diet supplement with indicated vt₂ hormone.

The claims defining the invention are as follows:

1. A treatment method comprising the step of treating a subject in need of such treatment with an effective weight gain preventative amount of $\Delta 5$ -androstene $3\beta, 7\alpha, 17\beta$ -triol, $\Delta 5$ -androstene $3\beta, 17\beta$ -diol-7-one, or a derivative thereof wherein at least one of the 5 hydroxyl groups is esterified with a C_{2-22} aliphatic acid, a C_{7-12} aromatic acid, a C_3 or greater dicarboxylic acid in which only one of the carboxyl groups is esterified to the hydroxyl group(s) on the steroid; or an inorganic acid.
2. The treatment of claim 1, wherein the step of treating a subject comprises the step of treating a mammal.
- 10 3. The treatment method of claim 2, wherein the step of treating a mammal comprises the step of treating a human.
4. The treatment method of any one of claims 1 to 3, wherein the amount is about 0.1 to about 2 grams of steroid per 100kg body weight per day.
5. The treatment of any one of claims 1 to 3, wherein the amount is about 0.5 to 15 2 grams of the steroid per 100kg body weight per day.
6. The treatment method of any one of claims 1 to 3, wherein the steroid is administered to the subject at least once a week.
7. The treatment method of any one of claims 1 to 4, wherein the steroid is administered to the subject at least once a day.
- 20 8. The treatment method of any one of claims 1 to 7, wherein the steroid is injected.
9. The treatment method of any one of claims 1 to 7, wherein the steroid is ingested.
10. A treatment method comprising the step of treating an overweight subject in 25 need of such treatment with an effective weight reduction promoting amount of $\Delta 5$ -androstene $3\beta, 7\alpha, 17\beta$ -triol, $\Delta 5$ -androstene $3\beta, 17\beta$ -diol-7-one, or a derivative thereof wherein at least one of the hydroxyl groups is esterified with a C_{2-22} aliphatic acid, a C_{7-12} aromatic acid, a C_3 or greater dicarboxylic acid in which only one of the carboxyl groups is esterified to the hydroxyl group(s) on the steroid; or an inorganic acid.
- 30 11. A method of treating obesity comprising the step of treating an obese subject with a therapeutic amount of $\Delta 5$ -androstene $3\beta, 7\alpha, 17\beta$ -triol, $\Delta 5$ -androstene $3\beta, 17\beta$ -diol-7-one, or a derivative thereof wherein at least one of the hydroxyl groups is esterified with a C_{2-22} aliphatic acid, a C_{7-12} aromatic acid, a C_3 or greater dicarboxylic acid in which only one of the carboxyl groups is esterified to the hydroxyl group(s) on the 35 steroid; or an inorganic acid.
12. A treatment procedure effective for promoting weight loss which comprises the step of treating an overweight subject with an effective weight reduction promoting amount of $\Delta 5$ -androstene $3\beta, 7\alpha, 17\beta$ -triol, $\Delta 5$ -androstene $3\beta, 17\beta$ -diol-7-one, or a derivative thereof wherein at least one of the hydroxyl groups is esterified with a C_{2-22}

aliphatic acid, a C₇-12 aromatic acid, a C₃ or greater dicarboxylic acid in which only one of the carboxyl groups is esterified to the hydroxyl group(s) on the steroid; or an inorganic acid.

13. A treatment method comprising the step of treating a subject in need of such treatment with an effective weight gain preventative amount of Δ5-androstene 3β-ol-7,17-dione, Δ5-androstene 3β,7-diol-17-one, or a derivative thereof wherein at least one of the hydroxyl groups is esterified with a C₂-22 aliphatic acid, a C₇-12 aromatic acid, a C₃ or greater dicarboxylic acid in which only one of the carboxyl groups is esterified to the hydroxyl group(s) on the steroid; or an inorganic acid.

10 14. A treatment method comprising the step of treating a subject in need of such treatment with an effective weight reduction promoting amount of Δ5-androstene 3β-ol-7,17-dione, Δ5-androstene 3β,7-diol-17-one, or a derivative thereof wherein at least one of the hydroxyl groups is esterified with a C₂-22 aliphatic acid, a C₇-12 aromatic acid, a C₃ or greater dicarboxylic acid in which only one of the carboxyl groups is esterified to the hydroxyl group(s) on the steroid; or an inorganic acid.

15 15. A method of treating obesity comprising the step of treating an obese subject with a therapeutic amount of Δ5-androstene 3β-ol-7,17-dione, Δ5-androstene 3β,7-diol-17-one, or a derivative thereof wherein at least one of the hydroxyl groups is esterified with a C₂-22 aliphatic acid, a C₇-12 aromatic acid, a C₃ or greater dicarboxylic acid in which only one of the carboxyl groups is esterified to the hydroxyl group(s) on the steroid; or an inorganic acid.

16. A treatment procedure effective for promoting weight loss which comprises the step of treating an overweight subject with an effective weight reduction promoting amount of Δ5-androstene 3β-ol-7,17-dione, Δ5-androstene 3β,7-diol-17-one, or a derivative thereof wherein at least one of the hydroxyl groups is esterified with a C₂-22 aliphatic acid, a C₇-12 aromatic acid, a C₃ or greater dicarboxylic acid in which only one of the carboxyl groups is esterified to the hydroxyl group(s) on the steroid; or an inorganic acid.

17. A biologically active steroid effective for inhibiting weight gain without inducing a suppression of the appetite or promoting the synthesis of sex hormones comprising Δ5-androstene 3β,7α,17β-triol or a derivative thereof wherein at least one of the hydroxyl groups is esterified with a C₂-22 aliphatic acid, a C₇-12 aromatic acid, a C₃ or greater dicarboxylic acid in which only one of the carboxyl groups is esterified to the hydroxyl group(s) on the steroid; or an inorganic acid.

35 18. A biologically active steroid effective for inhibiting weight gain without inducing a suppression of the appetite or promoting the synthesis of sex hormones comprising Δ5-androstene 3β,17β-diol-7-one, or a derivative thereof wherein at least one of the hydroxyl groups is esterified with a C₂-22 aliphatic acid, a C₇-12 aromatic acid, a

C_3 or greater dicarboxylic acid in which only one of the carboxyl groups is esterified to the hydroxyl group(s) on the steroid; or an inorganic acid.

19. A biologically active Δ^5 -androstene $3\beta,7\alpha$ -diol-17-one substantially as herein described with reference to Example I, Δ^5 -androstene 3β -7($\alpha\beta$)-diol-17-one substantially as herein described with reference to Example II, Δ^5 -androstene 3β -ol-7,17-dione substantially as herein described with reference to Example III, Δ^5 -androstene $3\beta,7,17$ -triol substantially as herein described with reference to Example IV, Δ^5 -androstene $3\beta,7$ -($\alpha\beta$),17 β -triol substantially as herein described with reference to Example V, Δ^5 -androstene $3\beta,17(\beta)$ -diol-7-one substantially as herein described with reference to Example VI or a derivative of any one of the foregoing effective for inhibiting weight gain without inducing a suppression of the appetite or promoting the synthesis of sex hormones.

20. A pharmaceutical composition for inhibiting weight gain in a subject comprising a steroid of any one of claims 17 to 19, together with a pharmaceutically acceptable carrier, diluent or adjuvant therefor.

21. A method for inhibiting weight gain in a subject comprising the step of treating a subject in need of such treatment with an effective amount of a steroid of any one of claims 17 to 19 or a composition of claim 20 for inhibiting weight gain without inducing a suppression of the appetite or promoting the synthesis of sex hormones.

22. A process for making a biologically active Δ^5 -androstene $3\beta,7\alpha$ -diol-17-one substantially as herein described with reference to Example I, Δ^5 -androstene 3β -7($\alpha\beta$)-diol-17-one substantially as herein described with reference to Example II, Δ^5 -androstene 3β -ol-7,17-dione substantially as herein described with reference to Example III, Δ^5 -androstene $3\beta,7,17$ -triol substantially as herein described with reference to Example IV, Δ^5 -androstene $3\beta,7$ -($\alpha\beta$),17 β -triol substantially as herein described with reference to Example V, Δ^5 -androstene $3\beta,17(\beta)$ -diol-7-one substantially as herein described with reference to Example VI or a derivative of any one of the foregoing effective for inhibiting weight gain without inducing a suppression of the appetite or promoting the synthesis of sex hormones.

30

Dated 7 January, 1994
Humanetics Corporation

Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER: _____**

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.